(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 October 2004 (28.10.2004)

PCT

(10) International Publication Number
WO 2004/092126 A3

(51) International Patent Classification[7]: C07D 207/16

(21) International Application Number: PCT/US2004/011253

(22) International Filing Date: 9 April 2004 (09.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/462,795 14 April 2003 (14.04.2003) US

(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CVETOVICH, Raymond** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **CHUNG, John, Y.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **AMATO, Joseph, S.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **DIMICHELE, Lisa** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with amended claims and statement*

(88) Date of publication of the international search report: 20 January 2005

Date of publication of the amended claims and statement: 31 March 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS AND INTERMEDIATES FOR THE PREPARATION OF PYRROLIDINE CARBOXYLIC ACIDS

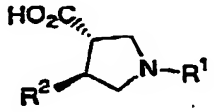
(57) Abstract: A novel process is provided for the preparation of pyrrolidine carboxylic acids, and the useful intermediates obtained therein. These compounds are intermediates for the synthesis of melanocortin-4 receptor (MC-4R), which are useful for the treatment of disorders such as obesity, diabetes, male sexual dysfunction, and female sexual dysfunction.

WO 2004/092126 A3

AMENDED CLAIMS
[received by the International Bureau on 19 November 2004 (19.11.04);
claim 31 deleted; claim 39 new;
original claim 34 replaced by amended claim 34;
remaining claims unchanged]

23. The process of Claim 22 wherein R^2 is *ortho, para*-difluorophenyl.

24. The process of Claim 1 wherein the compound of structural formula (I) is isolated by forming a zwitterion of the trans pyrrolidine acid of structural formula (I)



(I)

wherein R^1 and R^2 are as defined above; recrystallizing the zwitterion from a solvent; and isolating the resulting product.

25. The process of Claim 24 wherein the zwitterion of the pyrrolidine acid of formula (I) is formed at the isoelectric pH using an acid.

26. The process of Claim 25 wherein the acid is selected from sulfuric acid or hydrochloric acid.

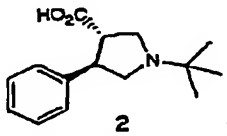
27. The process of Claim 26 wherein the acid is sulfuric acid.

28. The process of Claim 24 wherein the zwitterion of the pyrrolidine acid of formula (I) is recrystallized from a solvent.

29. The process of Claim 28 wherein the solvent is selected from the group consisting of ethanol, isopropyl alcohol, methyl *tert*-butyl ether or a mixture thereof.

30. The process of Claim 29 wherein the solvent is a mixture of 1:3 isopropyl alcohol:methyl *tert*-butyl ether.

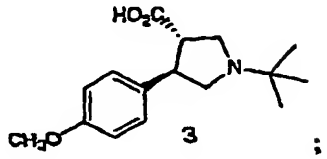
32. The compound 2



2 ;

or a zwitterion or salt thereof.

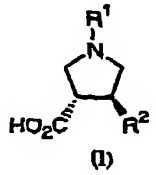
33. The compound 3



3 ;

or a zwitterion or a salt thereof.

34. A process for the preparation of compounds of structural formula (I):



(I)

wherein

R^1 is selected from the group consisting of

(1) hydrogen,
(2) amidino,
(3) C_{1-4} alkyliminoyl,
(4) C_{1-10} alkyl,
(5) $-(CH_2)_n$-C_{3-7} cycloalkyl,
(6) $-(CH_2)_n$-phenyl,
(7) $-(CH_2)_n$-naphthyl, and
(8) $-(CH_2)_n$-heteroaryl,

in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3; and alkyl, cycloalkyl, and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo;

R^2 is selected from the group consisting of

(1) C_{1-4} alkyl,
(2) $-(CH_2)_n$-cycloalkyl,
(3) $-(CH_2)_n$-heterocycloalkyl,

(4) $-(CH_2)_n$-phenyl,
(5) $-(CH_2)$n-naphthyl, and
(6) $-(CH_2)$n-heteroaryl wherein heteroaryl is selected from the group consisting of
(1) pyridinyl,
(2) furyl,
(3) thienyl,
(4) pyrrolyl,
(5) oxazolyl,
(6) thiazolyl,
(7) imidazolyl,
(8) pyrazolyl,
(9) isoxazolyl,
(10) isothiazolyl,
(11) pyrimidinyl,
(12) pyrazinyl,
(13) pyridazinyl,
(14) quinolyl,
(15) isoquinolyl,
(16) benzimidazolyl,
(17) benzofuryl,
(18) benzothienyl,
(19) indolyl,
(20) benzthiazolyl, and
(21) benzoxazolyl;

in which alkyl, phenyl, naphthyl, heteroaryl, and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from R^3;

each R^3 is independently selected from the group consisting of
(1) C_{1-6} alkyl,
(2) $-(CH_2)_n$-phenyl,
(3) $-(CH_2)_n$-naphthyl,
(4) $-(CH_2)_n$-heteroaryl,
(5) $-(CH_2)_n$-heterocycloalkyl,
(6) $-(CH_2)_n C_{3-7}$ cycloalkyl,
(7) halogen,

(8) OR^4,
(9) $-(CH_2)_nN(R^4)_2$,
(10) NO_2,
(11) $-(CH_2)_nNR^4SO_2R^4$,
(12) $-(CH_2)_nSO_2N(R^4)_2$,
(13) $-(CH_2)_nS(O)_pR^4$,
(14) CF_3,
(15) CH_2CF_3,
(16) OCF_3, and
(17) OCH_2CF_3;

in which heteroaryl is as defined above: alkyl, phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy; and wherein any methylene (CH_2) carbon atom in R^3 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl; or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R^4 is independently selected from the group consisting of

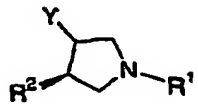
(1) hydrogen,
(2) C_{1-6} alkyl,
(3) $-(CH_2)_n$-phenyl,
(4) $-(CH_2)_n$-heteroaryl,
(5) $-(CH_2)_n$-naphthyl,
(6) $-(CH_2)_n$-heterocycloalkyl,
(7) $-(CH_2)_nC_{3-7}$ cycloalkyl, and
(8) $-(CH_2)_nC_{3-7}$ bicycloalkyl;

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy; or two R^4 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC_{1-4} alkyl; and

n is 0, 1, 2, 3 or 4;

comprising the steps of:

(a) hydrolyzing a pyrrolidine compound of structural formula (X), wherein Y is –CN or $-CO_2R^5$ and R^5 is C_{1-4} alkyl, and wherein R^1 and R^2 are as defined above,



(X)

with an aqueous base in a solvent; and

(b) isolating the resulting product.

35. The process of Claim 34 wherein the pyrrolidine compound of formula (X) is hydrolyzed with a base selected from the group consisting of NaOH, LiOH and KOH.

36. The process of Claim 35 wherein the base is aqueous NaOH.

37. The process of Claim 36 wherein R^2 is selected from the group of phenyl; *ortho, para*-difluorophenyl; and *para*-methoxyphenyl.

38. The process of Claim 37 wherein R^2 is *ortho, para*-difluorophenyl.

39. The process of Claim 34 wherein R^1 is *tert*-butyl.

Statement Under Article 19(1)

Claim 34 of the international application has been amended to recite Y is –CN or –CO2R5 and R5 is C1-4 alkyl. New Claim 39 of the international application has been added to recite R1 is *tert*-butyl. The amendment and new claim are fully supported by the Applicant's description. The present amendment and new claim have no impact on the description and the drawings of the international application.